Infectious Diseases Watch

March 21,2022

Ed Septimus, MD

General Infectious Disease

A Pragmatic Stepped-wedge, Cluster-controlled Trial of Real-time Pneumonia Clinical Decision Support Am J Respir Crit Care Med published online March 8, 2022

DOI: 10.1164/rccm.202109-2092OC

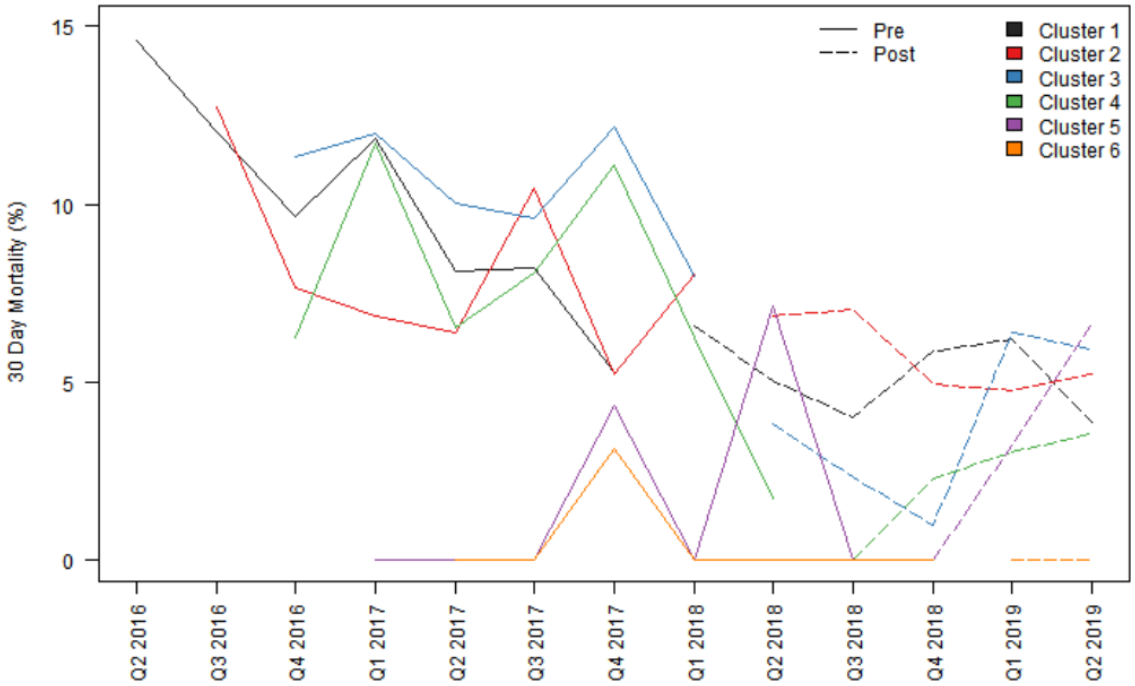
For this study, the researchers deployed the health system's electronic, open loop, clinical decision support (ePNa) system to 16 of its community hospitals between December 2017 to June 2019. During this time period, those hospitals had 6,848 pneumonia cases, and ePNa was used by a bedside clinician in 67% of eligible patients.

The Intermountain decision support tool gathers key patient indicators including age, fever, oxygen saturation, laboratory and chest imaging results, and vital signs to made recommendations on care, including appropriate antibiotic therapy, microbiology studies, and care setting recommendations (i.e., whether a patient should be sent to the ICU, admitted to the hospital, or is safe to go home).

ePNa first identifies ED patients with possible pneumonia based on their presenting symptoms, coded nurse exam findings, laboratory, and radiographic findings. A Bayesian probabilistic algorithm calculates and displays percent likelihood of pneumonia and the pertinent data elements directly to ED clinicians. ePNa alerts clinicians when pneumonia probability is ≥ 40%. The clinician chooses either to launch ePNa or not. ePNa then calculates illness severity using automated versions of established tools: (eCURB), calculated arterial blood oxygenation compared to inspired oxygen fraction (PaO2/FiO2) from percutaneous oxygen saturation (SpO2). ePNa uses arterial blood gas measurement of PaO2 preferentially when available. Last the tool tabulates the 9 minor criteria for severe pneumonia (sCAP-see March 7, 2022, ID Watch).

Using the tool, Intermountain researchers found a range of positive outcomes for patients, including a 38% relative reduction in mortality 30 days after being diagnosed with pneumonia, with the largest reduction in mortality in patients admitted directly from the emergency department to the ICU; a 17% increase in outpatient disposition; a decrease in ICU admission without safety concerns; and a reduced mean time from emergency department admission to start of first antibiotic. Most inpatients receive ceftriaxone plus intravenous azithromycin. Vancomycin and cefepime replace ceftriaxone for patients with a DRIP score >3[Chest 2019;

843:843-851], linked with a recommendation for blood and sputum/tracheal aspirate cultures and urine antigens for legionella and pneumococcus. Patients given vancomycin also receive a nasal swab for MRSA; vancomycin is usually discontinued after the initial dose when the swab is negative.

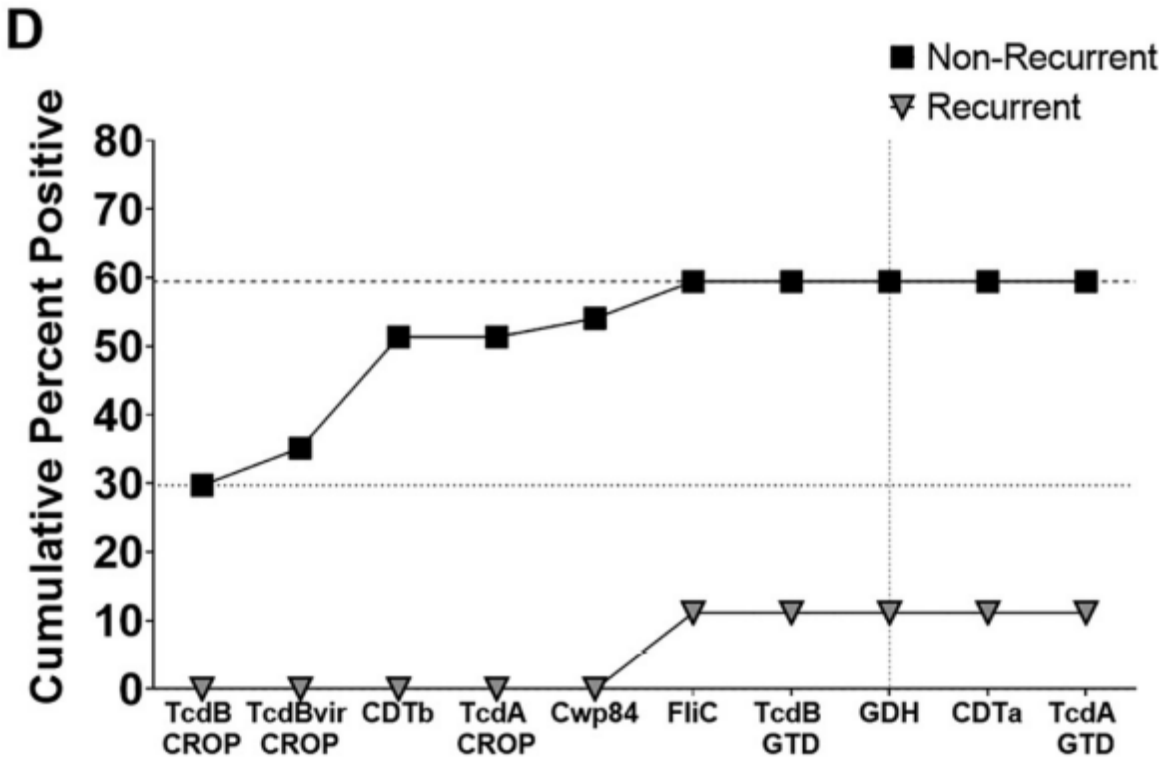


Comment: Unfortunately, the use of broad-spectrum antibiotics active against MRSA and/or *P. aeruginosa* within 8 hours was not significantly different, with 27% before and 25% after ePNa deployment, after severity adjustment OR 0.88 (0.75, 1.04), P=0.14. They also claimed this is a real-world validation of the 2007 and 2019 ATS/IDSA pneumonia treatment guidelines on which ePNa logic is based. Some of the observed residual broad spectrum antibiotic use was attributabled to early prescribing for sepsis prior to chest imaging, as well as antibiotic allergy history. There does not seem to be any microbiology in report and the term HCAP was used for the ePNa tool despite both ATS and IDSA eliminating the category. Multiple studies on CAP have documented that MRSA and Pseudomonas are uncommon causes of CAP, but about ¼ of patients in this study still received a drug active against MRSA and/or Pseudomonas. In the Inspire trial presented at ID Week 2021, the investigators used an algorithm to predict >10% resistance and/or risk for Pseudomonas for CAP. Based on baseline data for CAP (not ICU bound) <5% had either MRSA and/or Pseudomonas. In article reviewed in iD Watch March 7, 2022 [CCM published online February 2022] for patients with sCAP 10% were resistant to first-line CAP antibiotics and only 3.1% were resistant for non sCAP. I do not see mention of C *difficile* or other ADE. Their decision not to randomize by cluster may have affected the results. Patients were identified after their encounters by pneumonia discharge codes plus ED radiographic imaging; a method with high specificity but sensitivity of 68% versus physician review.

Detection of Newly Secreted Antibodies Predicts Nonrecurrence in Primary *Clostridioides difficile* Infection J Clin Microbiol 2022; 60: e02201-21

A novel immunoassay capable of detecting recently activated antibody-secreting cells (ASCs) derived from activated B lymphocytes in response to CD infection (Medium Enriched for Newly Synthesized Antibodies [MENSA]) was utilized to evaluate antibodies to 10 CD antigens in patients with and without CD recurrence. The antigen repertoire included the combined repetitive oligopeptide (CROP) and glucosyltransferase (GTD) domains of the secretory toxins TcdA and TcdB, the CROP domain of TcdB associated with hypervirulent *C. difficile* strains (TcdBvir-CROP), the A (CDTa) and B (CDTb) subunits of the secreted binary toxin CDT, flagellin (FliC), a major cell wall protein (Cwp84), and GDH. Three secreted toxin antigens (TcdB-CROP, TcdBvir-CROP, and CDTb) were the most effective for discriminating nonrecurrent from recurrent patients in both MENSA and serum. Blood samples were collected at 1, 2, and 4 weeks after infection; serum, ASCs, and MENSA were isolated.

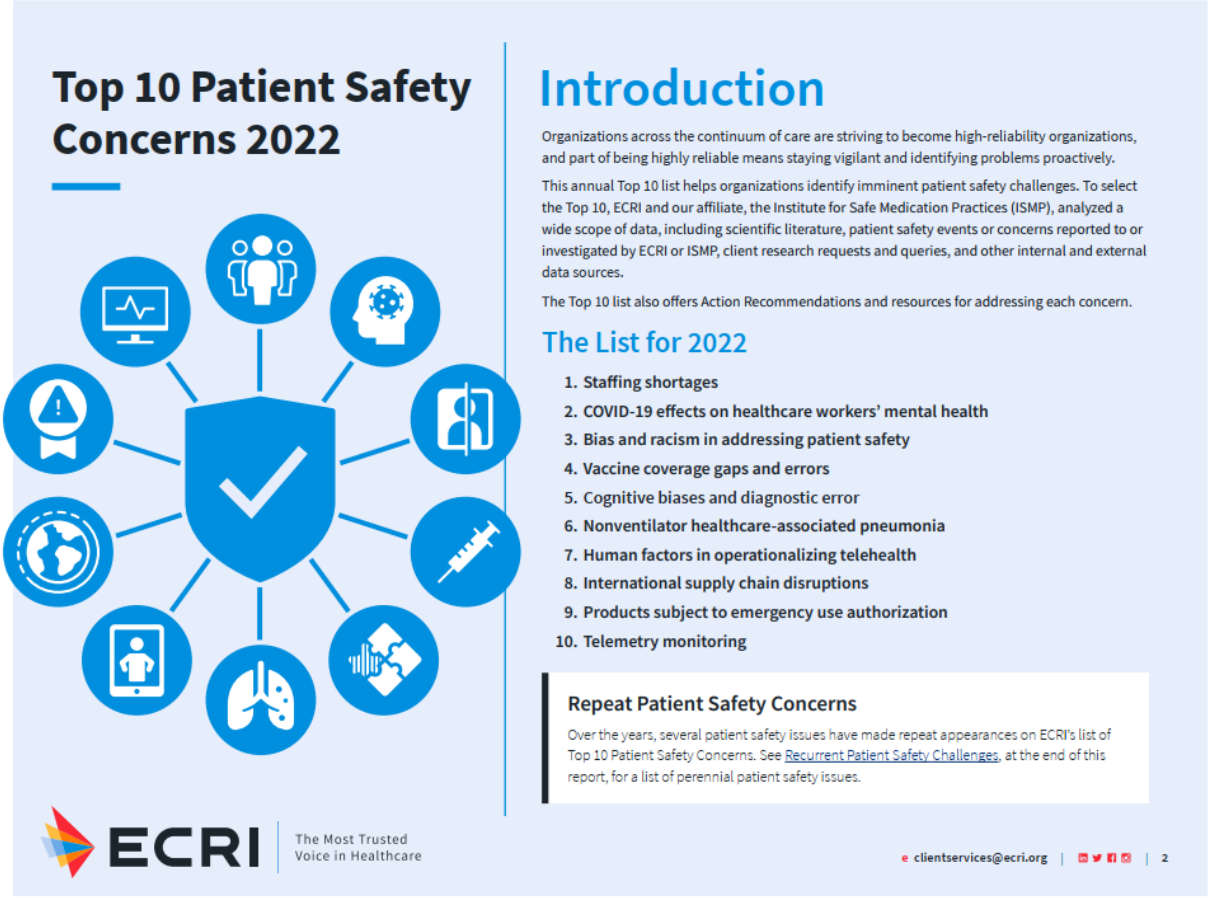
Among 46 patients with primary CD, 9 (20%) experienced recurrence within 8 weeks. Of the 37 patients without recurrence, 23 (62%) produced anti-CD antibodies against 3 of the 10 antigens. Serum responses showed a similar trend but were less sensitive, identifying only 19 responders (51%). Among the 9 patients with recurrence, none developed antibodies against the 3 CD antigens. Hence, a negative MENSA assay against all 3 antigens incurred a 19-fold increased risk for recurrence.



Comment: In conclusion, we propose a new strategy for stratifying patients during primary CDI into those at low versus higher risk for recurrence. The model measures the host immune

response as a clinical prediction tool for recognizing CDI patients who are not at risk for recurrence, thereby enabling preventative measures to be directed to patients who would derive maximal benefit.

ECRI Top Patient Safety Concerns 2022 report provided by Ken Sands



Top 10 Patient Safety Concerns 2022

Introduction

Organizations across the continuum of care are striving to become high-reliability organizations, and part of being highly reliable means staying vigilant and identifying problems proactively.

This annual Top 10 list helps organizations identify imminent patient safety challenges. To select the Top 10, ECRI and our affiliate, the Institute for Safe Medication Practices (ISMP), analyzed a wide scope of data, including scientific literature, patient safety events or concerns reported to or investigated by ECRI or ISMP, client research requests and queries, and other internal and external data sources.

The Top 10 list also offers Action Recommendations and resources for addressing each concern.

The List for 2022

1. Staffing shortages
2. COVID-19 effects on healthcare workers' mental health
3. Bias and racism in addressing patient safety
4. Vaccine coverage gaps and errors
5. Cognitive biases and diagnostic error
6. Nonventilator healthcare-associated pneumonia
7. Human factors in operationalizing telehealth
8. International supply chain disruptions
9. Products subject to emergency use authorization
10. Telemetry monitoring

Repeat Patient Safety Concerns

Over the years, several patient safety issues have made repeat appearances on ECRI's list of Top 10 Patient Safety Concerns. See Recurrent Patient Safety Challenges, at the end of this report, for a list of perennial patient safety issues.

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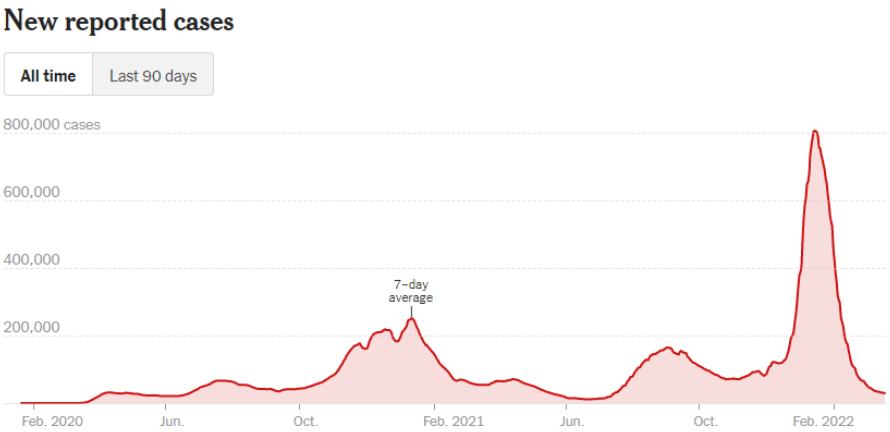
Comment: Staffing shortages and Covid-19 impact on HCW mental health highlights the impact on healthcare discussed several times in prior issues of ID Watch and Covid-19 Briefing. Supply chain is in the top 10 and nonventilated HAP(nHAP) made the top 10 as well. As has been reported in an article reviewed in ID Watch January 24, 2022[CID 2021;73:1013-1019], only about 1/3 of HAP were VAP. There is a need to study effective infection prevention strategies to prevent nHAP.

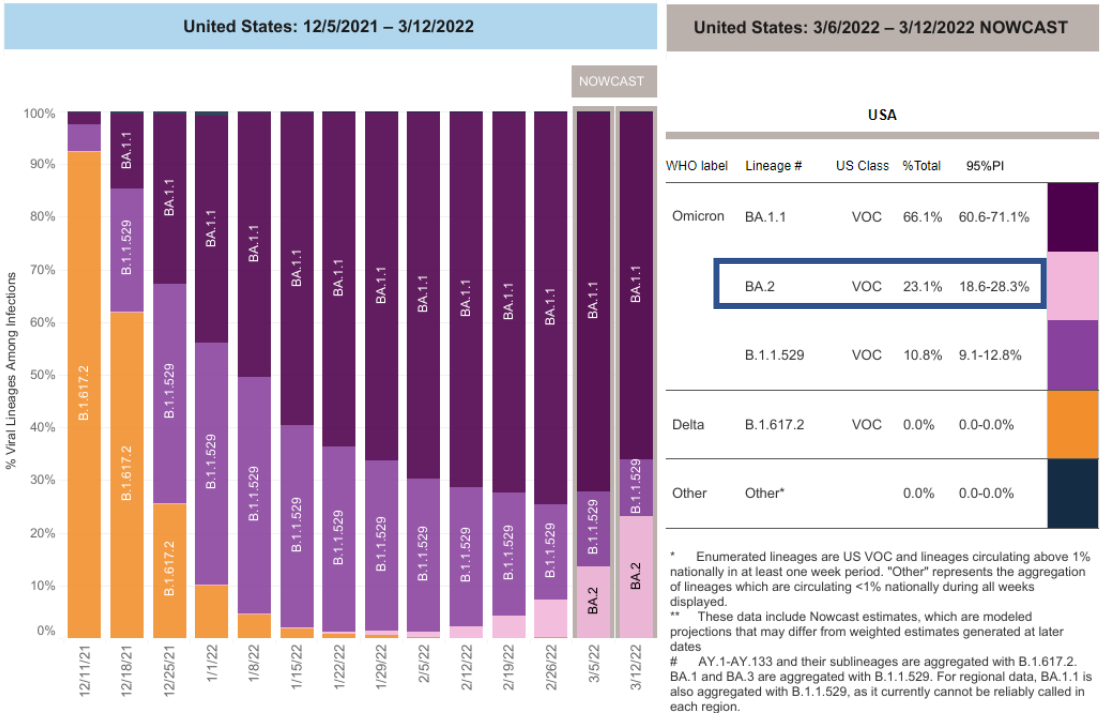
COVID-19

COVID-19 News

COVID-19 By the Numbers



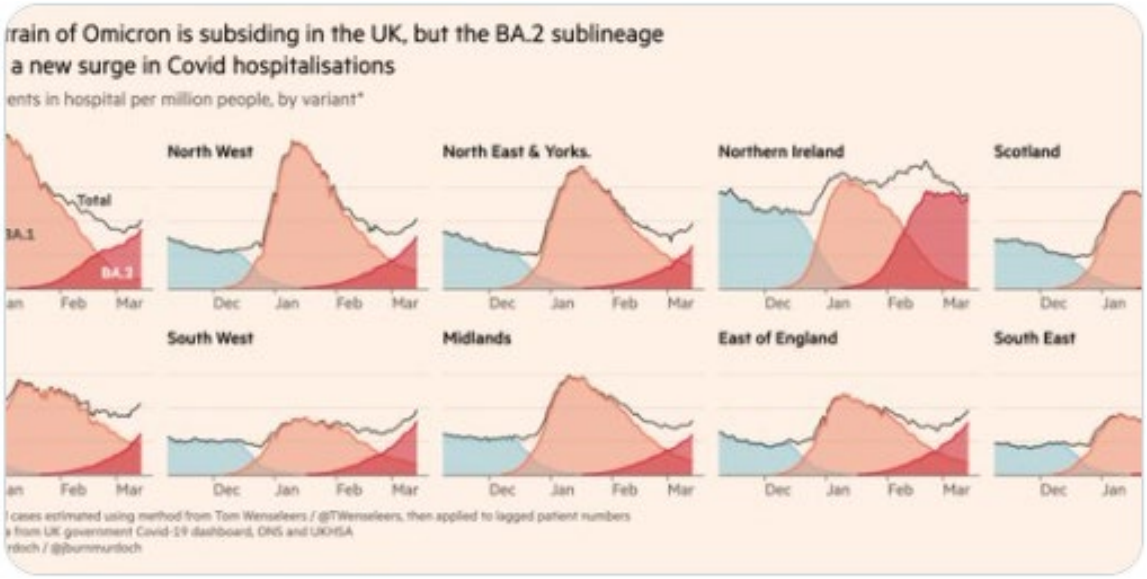
	DAILY AVG. ON MAR. 19	14-DAY CHANGE	TOTAL REPORTED
Cases	29,715	-35%	79,616,279
Tests	994,891	+5%	—
Hospitalized	20,086	-50%	—
In I.C.U.s	3,475	-54%	—
Deaths	1,127	-27%	969,999



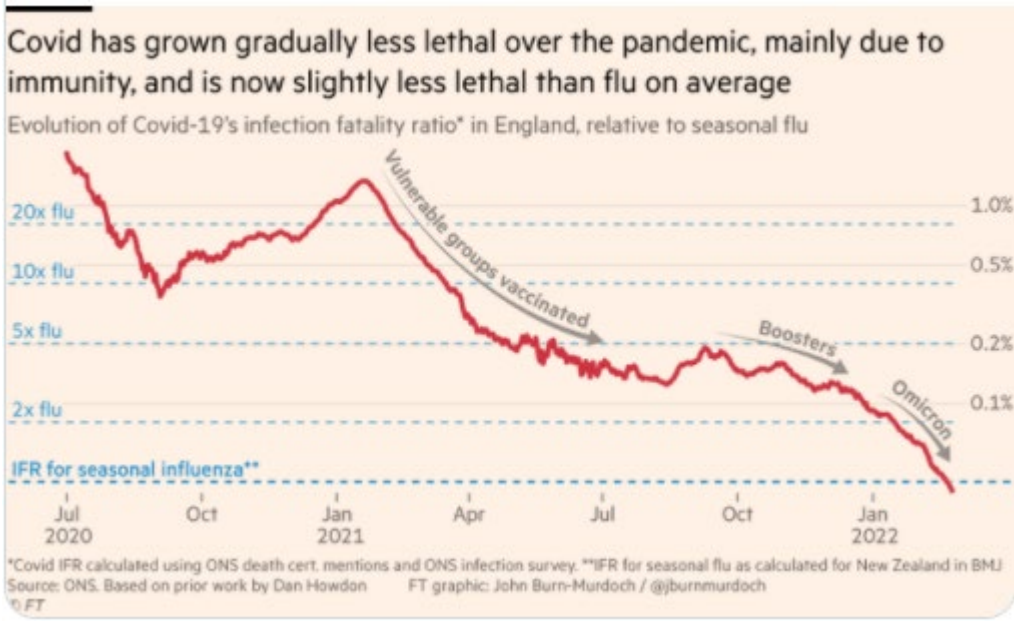
Will US Covid-19 Cases start to rise as BA.2 increases? (See variant graph above)

My short answer is I do not know. The BA.2 subvariant combined with society's reopening and waning immunity from vaccination or prior infection are driving a simultaneous increase of cases and hospitalizations in the UK All three of those factors are currently potential present in the US.

The basic reproduction number for BA.1 is about 8.2 and is nearly 12 for BA.2 (more transmissible) In the US, CDC estimate BA.2 increased from 1% of cases in early February to 23% by mid-March. UK health officials reported the BA.1 and BA.2 variants are similarly susceptible to vaccination, especially with a booster shot. The Omicron subvariant BA.2 appears to have the same severity as the original Omicron strain. Over 75% of strains in the UK are now BA.2 and hospitalizations were up 18 percent over the same period.



A potential warning comes from rising levels of virus in wastewater surveillance in some areas of the US and declining in other areas. We may see a bump up of infections as we lift restrictions and as BA.2 starts to spread and become more prevalent. I do not see a major wave, but this virus has surprised us many times in the last 2 years, so be vigilant. The graph below reported in the Financial Times last week shows the decline in Covid-19 deaths.



Ivermectin Didn't Reduce Covid-19 Hospitalizations in Largest Trial to Date WSJ March 19, 2022

The latest trial, of nearly 1,400 Covid-19 patients at risk of severe disease, is the largest to show that those who received ivermectin as a treatment didn't fare better than those who received a

placebo. Colleagues looked at 1,358 adults who visited one of 12 clinics in the Minas Gerais region of Brazil with Covid-19 symptoms. The patients all had a positive rapid test for SARS-CoV-2 and were at risk of having a severe case for reasons including a history of diabetes, hypertension, cardiovascular disease or lung disease. This was a perspective RCT-investigators prescribed half of the patients a course of ivermectin pills for three days. The other half received a placebo. They tracked whether the patients were hospitalized within 28 days. They also looked at whether patients on ivermectin cleared the virus faster than those who received a placebo, whether their symptoms resolved sooner, whether they were in the hospital or on ventilators for less time and whether there was any difference in the death rates for the two groups. Ivermectin didn't improve patient outcomes for any of these factors. This study has been accepted but has not been published online yet. This study was presented March 18th at a forum sponsored by the NIH.

Comments: This is a large, prospective study which should finally put to rest if ivermectin has value in the treatment of patients with early Covid-19 We are still waiting results of additional studies on fluvoxamine.

Inhaled Corticosteroids IDSA update March 18, 2022

Recommendation: Among ambulatory patients with mild-to-moderate COVID-19, the IDSA guideline panel suggests against inhaled corticosteroids outside of the context of a clinical trial. (Conditional recommendation, Moderate certainty of evidence)

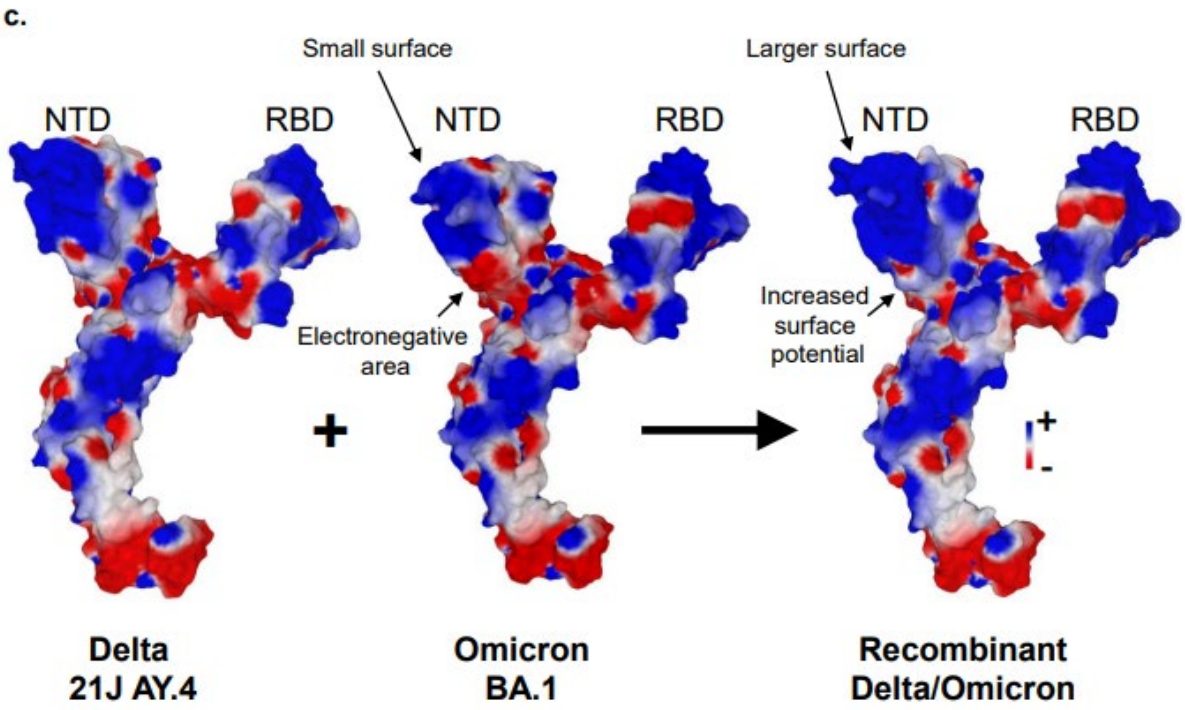
Among patients with mild-to-moderate COVID-19, inhaled corticosteroids failed to show or exclude a beneficial effect on mortality or COVID-19-related hospitalization (risk ratio [RR]: 0.61; 95% confidence interval [CI]: 0.22, 1.67; absolute risk reduction: 3 fewer per 1,000 [from 7 fewer to 6 more and RR: 0.67; 95% CI: 0.36, 1.26; Moderate certainty of evidence, respectively]; moderate certainty of evidence [CoE])

Journal Review

Culture and identification of a "Deltamicron" SARS-CoV-2 in a three cases cluster in 7 southern France medRxiv posted online March 8, 2022

doi.org/10.1101/2022.03.03.22271812

The investigators report three infections in southern France with a Delta 21J/AY.4-Omicron 21K/BA.1 "Deltamicron" recombinant. The hybrid genome harbors signature mutations of the two lineages, supported by a mean sequencing depth of 1,163-1,421 reads and mean nucleotide diversity of 0.1-0.6%. It is composed of the near full-length spike gene (from codons 156-179) of an Omicron 21K/BA.1 variant in a Delta 21J/AY.4 lineage backbone. It is similar to those reported for 15 other patients sampled since January 2022 in Europe. Finally, structural analysis of the recombinant spike suggested its hybrid content could optimize viral binding to the host cell membrane.



Comment: The new Deltacron COVID-19 variant does not initially appear to be any more severe than Omicron, or transmissible. The spike protein comes almost entirely from Omicron. The rest of the genome is Delta. The spike protein is the most important part of the virus when it comes to invading cells. It is also the main target of antibodies produced through infections and vaccines. So, the defenses that people have acquired against Omicron — through natural infection and/or vaccination should work just as well against the new recombinant. Like Omicron, Deltacron can evade monoclonal antibody treatment, however, approved treatments, like Paxlovid, molnupiravir, and remdesivir, remain effective if initiated shortly after COVID-19 diagnosis.

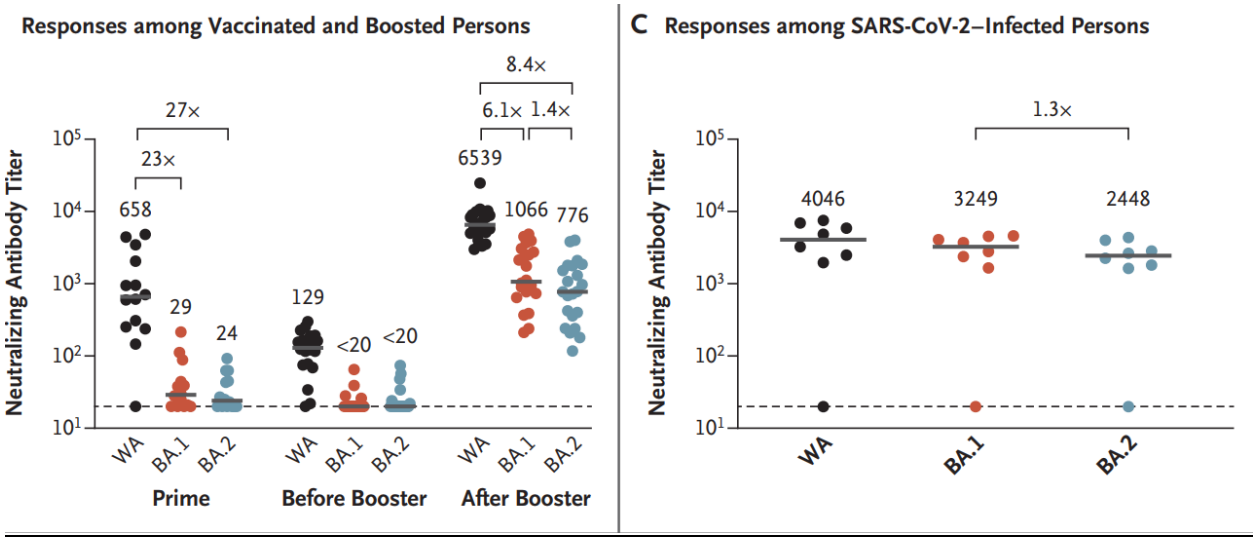
Neutralization of the SARS-CoV-2 Omicron BA.1 and BA.2 Variants N Engl J Med published online March 16, 2022

DOI: 10.1056/NEJMc2201849

The investigators evaluated neutralizing antibody responses against the ancestral strain of the virus, as well as against the omicron BA.1 and BA.2 variants, in 24 persons who had been vaccinated and boosted with the Pfizer vaccine and had not had infection with SARS-CoV-2 and in 8 persons with a history of SARS-CoV-2 infection, irrespective of vaccination status.

After the initial two doses of the Pfizer vaccine, the median pseudovirus neutralizing antibody titers against the ancestral, BA.1, and BA.2 were 658, 29, and 24, respectively, indicating that the median neutralizing antibody titer against the ancestral strain was 23 and 27 times those for BA.1 and BA.2, respectively. Six months after the initial vaccination, the median neutralizing antibody titers declined to 129 for the ancestral strain and to less than 20 for both BA.1 and BA.2. Two weeks after the third dose (booster) of the Pfizer vaccine, the median neutralizing antibody titers increased substantially to 6539 for the ancestral stain, 1066 for BA.1, and 776 for BA.2, indicating that the median neutralizing antibody titer against the ancestral strain was 6.1 and 8.4 times those for BA.1 and BA.2, respectively. The median BA.2 neutralizing antibody titer was lower than the median BA.1 neutralizing antibody titer by only a factor of 1.4.

The investigators next evaluated neutralizing antibody titers in the 8 persons with a history of SARS-CoV-2 infection at a median of 14 days after SARS-CoV-2 infection, which was diagnosed during a time when the omicron BA.1 was responsible for more than 99% of new infections. The median neutralizing antibody titers were 4046 for the ancestral strain, 3249 for BA.1, and 2448 for BA.2. The median BA.1 neutralizing antibody titer was 1.3 times the median BA.2 neutralizing antibody titer.



Comment: The data shows that neutralizing antibody titers against BA.2 were similar to those against BA.1, with median titers against BA.2 that were lower than those against BA.1 by a factor of 1.3 to 1.4. A third dose of the Pfizer vaccine was needed for induction of consistent neutralizing antibody titers against either BA.1 or BA.2. Moreover, in vaccinated persons who

had presumably been infected with BA.1, robust neutralizing antibody titers against BA.2 developed, which suggests a substantial degree of cross-reactive natural immunity. It is encouraging that vaccinated people who were infected with Omicron had high levels of antibodies that would probably also protect against BA.2. If that protection lasts, it could reduce the impact of a future wave, given the country's high levels of infection this winter.

The Advisory Committee on Immunization Practices' Recommendation for Use of Moderna COVID-19 Vaccine in Adults Aged ≥18 Years and Considerations for Extended Intervals for Administration of Primary Series Doses of mRNA COVID-19 Vaccines — United States, February 2022 MMWR 71:416–421

Data were also presented to ACIP regarding the optimal interval between the first and second dose of a Moderna or Pfizer mRNA primary vaccination series. mRNA COVID-19 vaccines are safe and effective at the authorized interval between the first and second doses (4 weeks for Moderna vaccine; 3 weeks for Pfizer vaccine), but an extended interval might be considered for some populations. An elevated risk for myocarditis and myopericarditis among mRNA COVID-19 vaccine recipients has been observed, particularly in adolescent and young adult males. Several studies in adolescents and adults have indicated the small risk for myocarditis associated with mRNA COVID-19 vaccines might be reduced and peak antibody responses and vaccine effectiveness might be increased with an interval longer than 4 weeks between the 2 primary series doses. In a population-based cohort study in Ontario, Canada, rates of myocarditis among persons aged ≥18 years were lower with an extended interval (>4 to <8 weeks and ≥8 weeks) compared with the shorter interval (3–4 weeks) between the first and second doses of a primary series for both Moderna and Pfizer vaccines. In several studies, neutralizing antibody titers were higher after an extended interval between doses in a primary mRNA vaccine series (range = 6–14 weeks), compared with a standard interval of 3–4 weeks. VE against infection and hospitalization was higher with an extended (6–8-week) interval than with a standard (3–4-week) interval. Based on this evidence presented to ACIP, CDC has provided guidance that an 8-week interval might be optimal for some adolescents and adults, especially for males aged 12–39 years.

Comment: Given this information, increasing the dosing interval to 8 weeks seems reasonable providing better response and lower risk of myocarditis. See next article

Myocarditis Following a Third BNT162b2 Vaccination Dose in Military Recruits in Israel JAMA published online March 17, 2022

doi:10.1001/jama.2022.4425

On August 15, 2021, the Israel Defense Forces (IDF) began administering a third dose of COVID-19 vaccine, using the Pfizer vaccine only. This study included all military personnel vaccinated with a third dose of the Pfizer vaccine until September 30, 2021, and diagnosed with myocarditis up to October 14, 2021. All suspected myocarditis cases in the IDF are referred to the hospital. Diagnosis was based on laboratory, electrocardiogram, echocardiography, and cardiac magnetic resonance imaging findings.

During the Pfizer booster vaccination rollout, 126,029 IDF members were vaccinated. Of the men, 79% were 18 to 24 years old and of the women, 90% were 18 to 24 years old. The age and sex distribution of vaccine recipients was similar to that of the general IDF population. During follow-up, only 9 members, all young men, were diagnosed with myocarditis. One case occurred after COVID-19 and was excluded. The 8 remaining cases had a negative result on a SARS-CoV-2 PCR test at the time of diagnosis. Four developed symptoms within a week of vaccination, 3 had symptoms beginning 8 to 10 days after vaccination, and 1 developed symptoms more than 2 weeks after vaccination (and thus was excluded from analysis). All cases were mild, without arrhythmia or signs of congestive heart failure. All remained without residual cardiac injury on hospital discharge.

The incidence rates of myocarditis in the week and 2 weeks following a third vaccine dose were 3.17 (95% CI, 0.64-6.28) and 5.55 (95% CI, 1.44-9.67) per 100,000 vaccines given, Because all myocarditis cases were in young men (18-24 years old), they estimated the incidence for this specific population to be 6.43 (95% CI, 0.13-12.73) and 11.25 (95% CI, 2.92-19.59) per 100,000 vaccines given in the week and 2 weeks after a third vaccine dose, respectively.

Comment: This study found a low risk of myocarditis after a third dose of the Pfizer in Israeli military recruits. The incidence was lower than observed a week after a second dose of the vaccine in a similar Israeli military population (5.07 per 100,000 vaccines vs 3.17) Because the study included only cases diagnosed in the hospital, there is a chance for underdiagnosis, and the incidence of myocarditis may be higher. The article above demonstrated the risk of myocarditis was also lower if the dosing interval was 8 weeks versus 3-4 weeks.

Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients With Mild to Moderate COVID-19 JAMA published online March 14, 2022

doi:10.1001/jama.2022.2832

This is a RCT involving 1057 nonhospitalized patients with symptomatic, mild to moderate COVID-19 and at least 1 risk factor for progression conducted at 57 sites in Brazil, Canada, Peru, Spain, and the US from August 27, 2020, through March 11, 2021. Patients were randomized (1:1) to an intravenous infusion with 500 mg of sotrovimab (n = 528) or placebo (n = 529). Eligible patients were aged 18 years or older, tested positive for SARS-CoV-2 by PCR or an antigen test, and had symptom onset within the prior 5 days. The primary outcome was the proportion of patients with COVID-19 progression through day 29 (all-cause hospitalization lasting >24 hours for acute illness management or death); secondary outcomes were tested in hierarchal order, including a composite of all-cause emergency department (ED) visit, hospitalization of any duration for acute illness management, or death through day 29 and progression to severe or critical respiratory COVID-19 requiring supplemental oxygen or MV.

All-cause hospitalization lasting longer than 24 hours or death was significantly reduced with sotrovimab (6/528 [1%]) vs placebo (30/529 [6%]) (adjusted relative risk [RR], 0.21 [95% CI, 0.09 to 0.50]; absolute difference, –4.53% [95% CI, –6.70% to –2.37%]; $P < .001$). Four of the 5 secondary outcomes were statistically significant in favor of sotrovimab, including reduced ED visit, hospitalization, or death (13/528 [2%] for sotrovimab vs 39/529 [7%] for placebo; adjusted

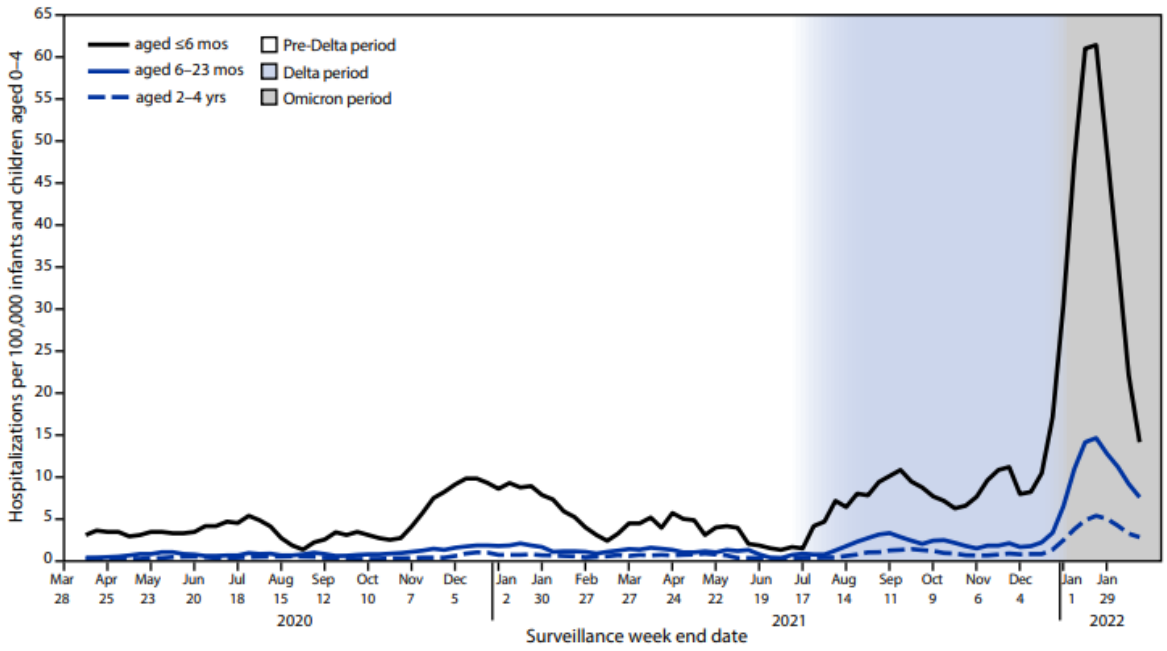
RR, 0.34 [95% CI, 0.19 to 0.63]; absolute difference, –4.91% [95% CI, –7.50% to –2.32%]; *P* < .001) and progression to severe or critical respiratory COVID-19 (7/528 [1%] for sotrovimab vs 28/529 [5%] for placebo; adjusted RR, 0.26 [95% CI, 0.12 to 0.59]; absolute difference, –3.97% [95% CI, –6.11% to –1.82%]; *P* = .002).

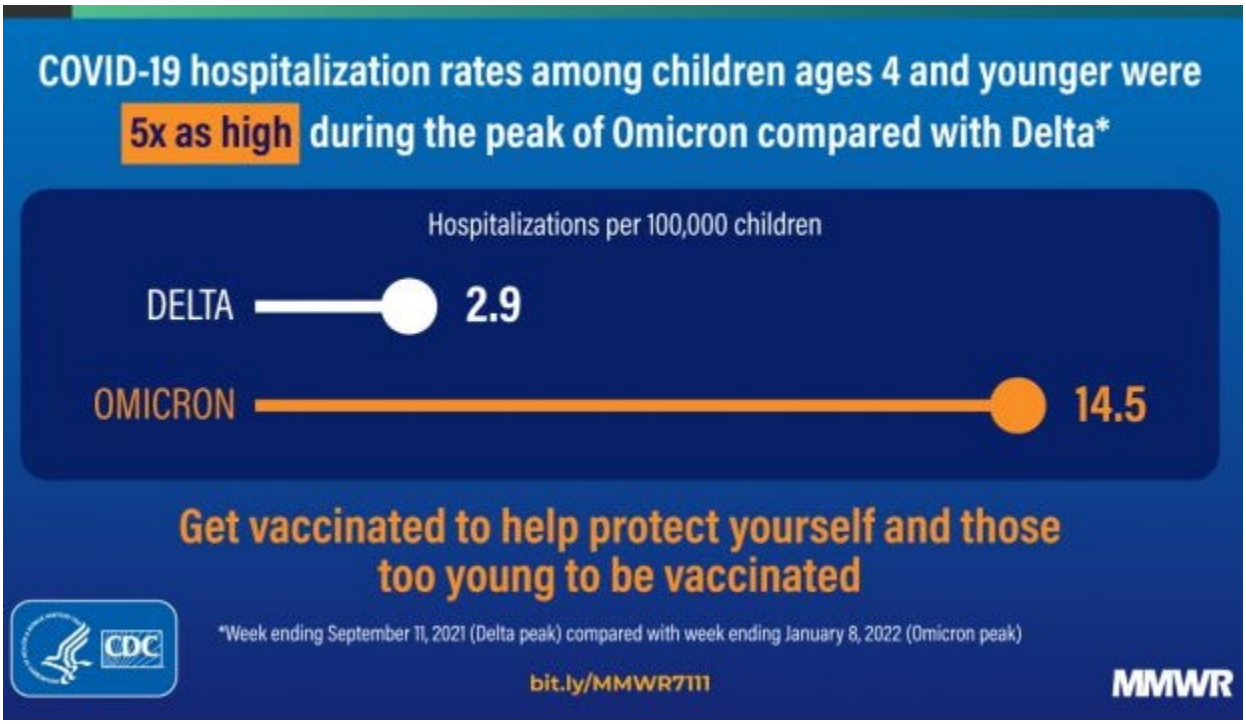
Comment: Findings support sotrovimab as a treatment option for nonhospitalized, high-risk patients with mild to moderate COVID-19. The study was done before Omicron, but invitro indicates activity against Omicron. In addition, this study used 5 days of symptoms. New recommendation for use of MCA is 7 days or less.

Hospitalization of Infants and Children Aged 0–4 Years with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 2020–February 2022

MMWR March 15, 2022

During the Omicron wave, US infants and children aged 0–4 years were hospitalized at approximately five times the rate of the previous peak during Delta. Infants aged <6 months had the highest rates of hospitalization, but indicators of severity (e.g., respiratory support) did not differ by age group. ICU admissions during Omicron predominance peaked at approximately 3.5 times the peak rate during Delta.





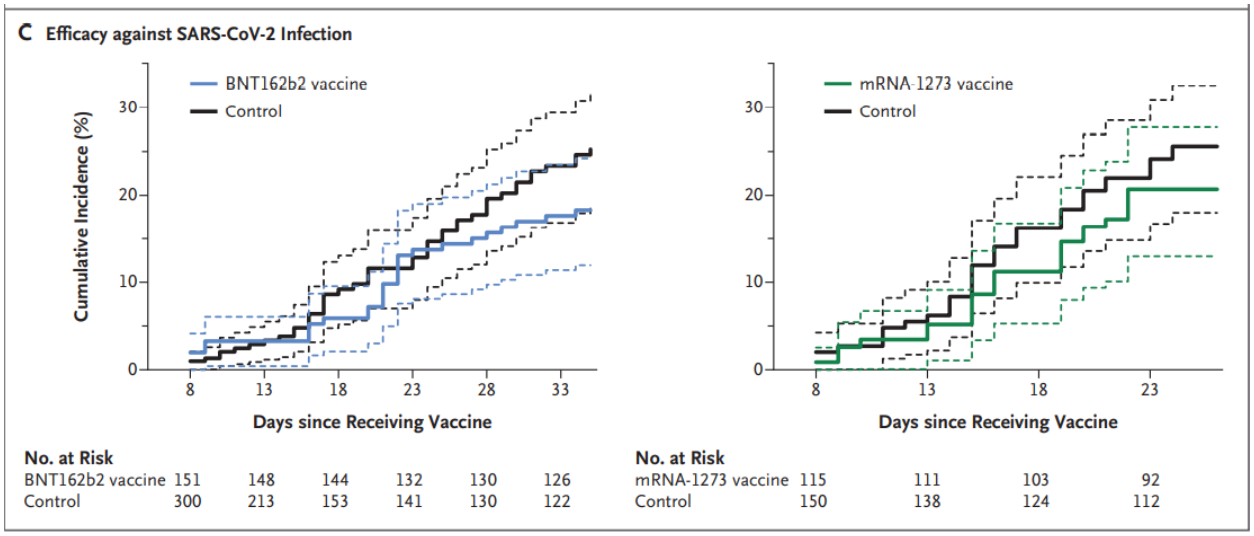
Comment: Although infants aged <6 months are not currently eligible for vaccination, the evidence suggests that this age group can receive protection through passive transplacental transfer of maternal antibodies acquired through vaccination and/or natural immunity. Important strategies to prevent COVID-19 among infants and young children until they can be vaccinated include vaccination of currently eligible populations such as pregnant women, family members, and caregivers of infants and young children.

Efficacy of a Fourth Dose of Covid-19 mRNA Vaccine against Omicron N Engl J Med published online March 16, 2022

DOI: 10.1056/NEJMc2202542

This study involved eligible health care workers enrolled in the Sheba HCW COVID-19 Cohort. 154 received the fourth dose of the Pfizer vaccine and, 1 week later, 120 received Moderna vaccine. For each participant, two age matched controls were selected from the remaining eligible participants. Fourth doses of both the Pfizer and Moderna vaccines produced an immune response, with both IgG antibodies against SARS-CoV-2 receptor-binding domain and neutralizing antibody titers increased by a factor of 9 to 10. Additionally, there was an increase in the live-virus neutralization of Omicron and other viral strains by a factor of about 10, however, the fourth dose added little on VE against the Omicron variant, in a real-world report from Israel. While a higher percentage of unboosted controls (25%) contracted Omicron versus those who received four doses of Pfizer (18%) or Moderna (21%), VE against any infection was only 30% for Pfizer (95% CI -9 to 55) and 11% for Moderna (95% CI -43 to 44). However, vaccine efficacy against symptomatic disease with Omicron was slightly higher, they noted, at

43% (95% CI 6.6-65.3) for Pfizer and 31% (95% CI -18.5 to 60.2) for Moderna, albeit with wide confidence intervals.



Comment: There has been much discussion and controversy around a fourth dose. Pfizer and Moderna area seeking EUA for a fourth dose (second booster) in adults. The results from this study suggest that maximal immunogenicity of mRNA vaccines is achieved after three doses and that antibody levels can be restored by a fourth dose. However, a fourth vaccination in healthy young health care workers may have only marginal benefits. Older and at-risk populations were not assessed, but more likely to benefit.